EXHIBIT B

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

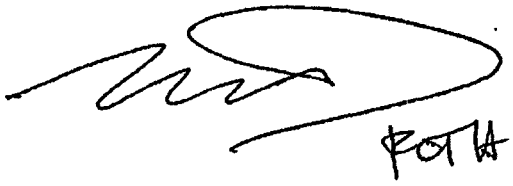
IN RE: ETHICON, INC. **PELVIC REPAIR SYSTEM** **PRODUCTS LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL No. 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

DEFENSE EXPERT GENERAL REPORT

of Ted Roth, M.D.:

TVT and TVT-O

Prepared by:



Ted Roth, M.D.

January 31, 2017

I. Qualifications and Experience

I am Board certified in Obstetrics & Gynecology with subspecialty Board certification in Female Pelvic Medicine and Reconstructive Surgery. After attending Johns Hopkins University as an undergraduate, I attended medical school at the University of Rochester and completed my residency in Obstetrics & Gynecology at Duke University under Charles Hammond. As a graduating resident, I received awards for outstanding surgical technique and outstanding laparoscopic skills. I continued my subspecialty training in Reconstructive Pelvic Surgery at the University of Mississippi Medical Center under G. Rodney Meeks.

I am Chief of Gynecology and the Medical Director of the Bladder Control Center at Central Maine Medical Center. I have implanted about 1,200 midurethral slings in total and currently perform 110-120 slings per year, approximately 90% of which are TVT-O and 10% of which are retropubic TVT. I also have extensive experience in managing sling complications.

I have presented numerous abstracts and posters at medical society meetings and published numerous articles in peer-reviewed medical journals, as well as book chapters on reconstructive pelvic surgery. I have also served as a reviewer for numerous peer-reviewed medical journals, including International Urogynecology Journal, Female Pelvic Medicine and Reconstructive Surgery, Journal of Urology, and the European Journal of Obstetrics & Gynecology and Reproductive Biology.

I have taught professional education courses and led cadaver labs on both SUI and POP products for Ethicon and have been on the speaker's bureau of Pfizer, GSK, Allergan, and Shionogi. I have also led professional education events for and served as a consultant for Medtronic.

My *curriculum vitae* is attached.

II. Materials Reviewed

All of my opinions set forth in this report are held to a reasonable degree of medical and scientific certainty and probability. My opinions are based on my clinical and surgical experience in both academic and community practice; my research and teaching; my analysis of the medical literature concerning the efficacy and safety of TVT and TVT-O; my review of medical society statements; my analysis of the Ethicon TVT and TVT-O Instructions for Use, professional education materials for users of TVT and TVT-O including surgical videos and anatomy animations, as well as the patient brochures; my participation in professional medical societies; discussions with peers at conferences and other professional events in my field; and my education and training. My opinions are also based on my review of deposition testimony and exhibits, expert reports (and the materials those reports cite to) as listed in the materials list attached to this report, and other materials, including materials issued by the FDA. A complete

list of the materials I have reviewed is attached to this report and will be supplemented as I review additional materials. My opinions and conclusions are based on the practice of evidence-based medicine. All of my opinions set forth in this report are held to a reasonable degree of medical and scientific certainty and probability.

III. Fees and Testimonial History

My fees for serving as an expert in this matter are $600 per hour for report writing, review and consultation. For deposition or court testimony, my fee is $800 per hour. As of the writing of this report, I have not yet provided expert testimony in the Ethicon pelvic mesh litigation.

IV. Opinions

A. Introduction/Stress urinary incontinence

Urinary incontinence is a very common condition in women. Almost 16% of community dwelling women in the US report symptoms of moderate to severe urinary incontinence. Broken down by age groups, moderate to severe SUI was reported to affect 6.9% of women 20 to 39 years old, 17.2% in 40 to 59 years old, 23.3% in those 60 to 79 years old, and 31.7% in women 80 years or older. (Nygaard I, et al., Prevalence of symptomatic pelvic floor disorders in US women, JAMA 2008 300(11): 1311-6.) Risk factors for incontinence include advancing age, higher parity, vaginal delivery, obesity, and post-menopausal status. (Ford AA et al., Mid-urethral sling operations for stress urinary incontinence in women, Cochrane Database Syst Rev 2015;7:CD006375).

SUI occurs when, during sudden increases of intra-abdominal forces, bladder pressure exceeds urethral closure pressure. Urine leakage may derive from loss of backstop support at the bladder neck (bladder-neck hypermobility) and / or from intrinsic sphincter deficiency (ISD), that is, the loss of muscular tone at rest. Current thinking has evolved away from this dichotomy with the understanding that patients are on a spectrum with some degree of hypermobility and ISD (Plzak L and Staskin D., Genuine stress incontinence theories of etiology and surgical correction, Urol Clin N Am 29 (2002) 527-535).

The International Continence Society defines stress urinary incontinence (SUI) as involuntary urine leakage on effort, exertion, sneezing, or coughing and mixed urinary incontinence (MUI) as involuntary leakage associated with urgency (a sudden, compelling desire to pass urine, which is difficult to defer), exertion, effort, sneezing, or coughing (www.icsoffice.org).

SUI is reported to account for 49% of female urinary incontinence, urgency incontinence for 22%, and MUI for 29% (Hannestad YS et al., A community-based epidemiological survey of

female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of incontinence in the county of nord-trondelag, J Clin Epidemiol 2000;53:1150–7). Although the prevalence of urinary incontinence may be surprisingly high, women often underreport or delay seeking treatment for several years after the problem has become bothersome because urinary incontinence can be a difficult topic for patients to discuss. (ACOG-AUGS Practice Bulletin No. 155, November 2015).

SUI results in significant personal and financial burden for symptomatic women. 75% of women who experience SUI report significant bother from their symptoms, and an estimated 13.6% of American women elect to undergo surgical treatment of SUI. (Wu JM, et al., Prevalence and trends of symptomatic pelvic floor disorders in U.S. women, Obstet Gynecol 2014; 123:141-148). Other management strategies to reduce the burden of SUI, especially for women with mild symptoms, include behavioral changes, weight reduction, some pessaries, and pelvic floor muscle therapy (PFMT).

Surgery is indicated as first-line treatment for appropriately counseled women who decline conservative treatment or when the patient has failed more conservative therapy in regards to symptom relief, and the patient desires further treatment in an effort to achieve continence. (ACOG Practice Bulletin No 63. Urinary Incontinence In Women)

Before midurethral slings (MUS) were developed in the late 1990s, most women who needed surgery for stress urinary incontinence (SUI) were treated with traditional procedures involving suturing of peri-urethral tissue to retropubic structures (colposuspension) or harvesting autologous material to place a sling under the urethra (pubovaginal slings). These surgical procedures, compared to the MUS, usually involve larger incisions, more or longer overnight hospital stays, prolonged recoveries, and more time off work, and place the patient at higher risk for major surgery complications like venous thromboembolism, wound infections, and potential hernias. (Nager C, Midurethral slings: evidence-based medicine vs the medicolegal system, Am J Obstet Gynecol June 2016, 708-711.) Pubovaginal slings also require an abdominal incision or incision in the thigh (or both) to harvest rectus fascia or fascia lata. Over time, the efficacy of these procedures decreases, leading many patients to re-operation.

B. The Development of the Midurethral Sling (MUS)

The concept of the TVT midurethral sling was based on Ulmsten and Petros's Integral Theory that anatomic defects in the connective tissue attachments of the urethra lead to urine leakage (Petros PE, Ulmsten U, An integral theory and its method for the diagnosis and management of female urinary incontinence, Scand J Urol Nephrol Suppl 1993, 153:1-93). Slings are placed to reinforce the lax pubourethral ligaments. Having already trialed Gore-Tex and Mersilene tapes with poor results, Ulmsten published his initial study on the use of a Prolene mesh sling, covered

by a plastic sheath and attached to needles, in 75 patients, in 1996. (Ulmsten U et al, An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence, Int Urogynecol J, 1996, 7:81-86.) Subsequent clinical trials further demonstrated the safety and efficacy of the TVT procedure including at five years' follow-up. (Rezapour M and Ulmsten U, Tension-free vaginal tape (TVT) in women with recurrent stress urinary incontinence – A long-term follow-up, Int Urogynecol J 2001 (Suppl 2):S9-S11; Rezapour M et al, Tension-free vaginal tape (TVT) in stress incontinent women with intrinsic sphincter deficiency (ISD) – A long-term follow-up, Int Urogynecol J 2001 (Suppl 2):S12-S14; Nilsson CG et al, Long-term results of the tension-free vaginal tape (TVT) procedure for surgical treatment of female stress urinary incontinence, Int Urogynecol J 2001 (Suppl 2):S5-S8.) The TVT-O, which delivers the ends of the sling through the obturator foramen and exit points through the thigh, features the same mesh as in the retropubic TVT and uses specially designed helical passers and a winged guide for placement. The TVT-O was developed by Jean De Leval and introduced on the market by Ethicon in 2004. Dr. De Leval developed the obturator approach sling to minimize the risk of urethral and bladder injury, and to minimize tissue dissection. Waltregny, De Leval, The TVT-obturator surgical procedure for the treatment of female stress urinary incontinence: a clinical update, Int Urogyn J 2009, 20:337–348.

The advent of the minimally invasive TVT midurethral sling (MUS) revolutionized the management of SUI. The needles allowed for minimally invasive placement via a vaginal incision; the plastic sheath minimized tissue damage during placement; the macroporous (> 75 microns), monofilament polypropylene mesh was tolerated well by patients; the tension-free placement reduced anchor-related complications of the Burch and other surgeries; the procedure was short and possible to perform under local anesthesia; and long-term cure rates were high. TVT and TVT-O also have a short learning curve, and the implant surgery techniques are standardized and reproducible.

Throughout the world, the MUS procedure became the standard surgical treatment for SUI. High success rates are consistently reported in numerous studies. In the most recent Cochrane Review on MUS for SUI, the authors concluded, "Mid-urethral sling operations have been the most extensively researched surgical treatment for SUI in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term." (Ford 2015.)

In the U.S., in the Urinary Incontinence Treatment Network Value of Urodynamic Evaluation trial, in which 53 urogynecologists or urologists could perform whatever procedure they wanted for SUI, 93% of the procedures were MUS. Surveys of members of the American Urogynecologic Society (AUGS) showed that even after 2011, 99% of AUGS members who did sling surgery for SUI used a MUS. (Nager CW et al., A randomized trial of urodynamic testing before stress-incontinence surgery, N Engl J Med 2012;366:1987-97) (Clemons JL et al., Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery, Female Pelvic Med Reconstr Surg 2013;19:191-8). The reason surgeons overwhelmingly prefer MUS such as TVT and TVT-O over the traditional repairs for SUI is that MUS are safer and more efficacious for patients, as has been

demonstrated by hundreds of studies. The efficacy of TVT has been demonstrated for at least 17 years. (Nilsson, CG, et al, Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence, Int Urogynecol J 2013, DOI 10.1007/s00192-013-2090-2.)

The FDA safety communication in 2011 specifically excluded MUS like TVT and TVT-O. On March 27, 2013, the FDA published "Considerations about Surgical Mesh for SUI," which noted that mesh sling procedures are currently the most common type of surgery performed to correct SUI, that the safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year, and that longer follow-up data is available in the literature. In 2016 the FDA specifically excluded mesh for SUI from its up-classification of transvaginal surgical mesh to treat pelvic organ prolapse.

In 2014, the board of directors from the professional medical societies AUGS and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) approved and unanimously endorsed a position statement on mesh MUS for SUI, which stated, "The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women." In June 2016, AUGS and SUFU updated the position statement, which was further endorsed by medical societies ACOG, AAGL and SGS, as well as two patient advocacy groups, Women's Health Foundation (WHF) and National Association for Continence (NAFC). I agree with both the 2014 and 2016 statements. Similar position statements supporting MUS have been released by other U.S. and international medical societies, including the International Urogynecological Association (Nager C, et al., Position statement on mesh midurethral slings for stress urinary incontinence, Female Pelvic Med Reconstr Surg 2014; 20:123-5) (IUGA, Position statement on mid-urethral slings for stress urinary incontinence, http://www.iuga.org/?page=mus) as well as the AUA (AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence (SUI), Oct. 2013 (revised), https://www.auanet.org/education/vaginal-mesh-for-sui.cfm), and the NICE (Urinary Incontinence: The management of urinary incontinence in women, Sept. 2013, https://www.nice.org.uk/guidance/cg171/chapter/1recommendations?unlid=72878330920168163120.)

Physicians like myself continue to perform MUS surgeries, despite TV advertisements for the pelvic mesh litigation, because we are practicing evidence-based medicine and know that the MUS is the best procedure for our patients. MUS, including TVT and TVT-O, are taught in residency and fellowship programs throughout the United States and are the gold standard procedure for SUI. To state otherwise would not reflect the reality of the surgical management of SUI today (Serati M, et al. Surgical treatment for female stress urinary incontinence: What is the gold-standard procedure? Int Urogynecol J 2009 20: 619-21).

I exclusively use Ethicon MUS (TVT and TVT-O).

Nager's 2016 paper on Midurethral slings: evidence-based medicine vs the medicolegal system, compared four meta-analyses to show that the overall data overwhelmingly favors MUS:

TABLE
Results of systematic reviews comparing midurethral slings with alternative stress urinary incontinence surgeries

MUS vs open retropubic colpopexy		
Favors MUS	**Favors both or no difference**	**Favors open retropubic colpopexy**
Overall cure rates[16] Objective cure rates[16] Blood loss[17] Postoperative pain[17] Operation time[17] Hospital stay[17] Bowel injury[17] Wound infection[17] Hematomas[17]	Objective cure rate by pad test[18] Subjective cure rate[16] Other complications besides bladder or vaginal perforations[16]	Bladder or vaginal perforations[16] Return to operating room for retention, erosion, OAB symptoms, groin pain[17]
MUS vs laparoscopic retropubic colpopexy		
Favors MUS	**Favors both or no difference**	**Favors laparoscopic colpopexy**
Objective cure rates[18] Operation time[18] Hospital stay[18]	Subjective cure rates	
MUS vs traditional (pubovaginal) sling		
Favors MUS	**Favors both or no difference**	**Favors pubovaginal sling**
Subjective cure rates[17] Storage lower urinary tract symptoms[16] Reoperation[16] Operation time[17,19] Blood loss[17] Hospital stay[17] Perioperative complications except for bladder perforation[19] Postoperative voiding dysfunction[19] Detrusor symptoms[19]	Overall cure rates[16] Subjective cure rates[16] Hematoma[16] Voiding lower urinary tract symptoms[16]	Bladder perforations[16] Vaginal perforation[17] Urinary tract infection[17]

MUS, midurethral sling.

Nager. Midurethral slings: evidence-based medicine vs medicolegal system. Am J Obstet Gynecol 2016.

[16. Novara G, Artibani W, Barber MD, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol 2010;58: 218-38.
17. Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and meta-analysis. Am J Obstet Gynecol 2014;211:71.e1-27.
18. Dean NM, Ellis G, Wilson PD, Herbison GP. Laparoscopic colposuspension for urinary incontinence in women. Cochrane Database Syst Rev 2006;3:CD002239.

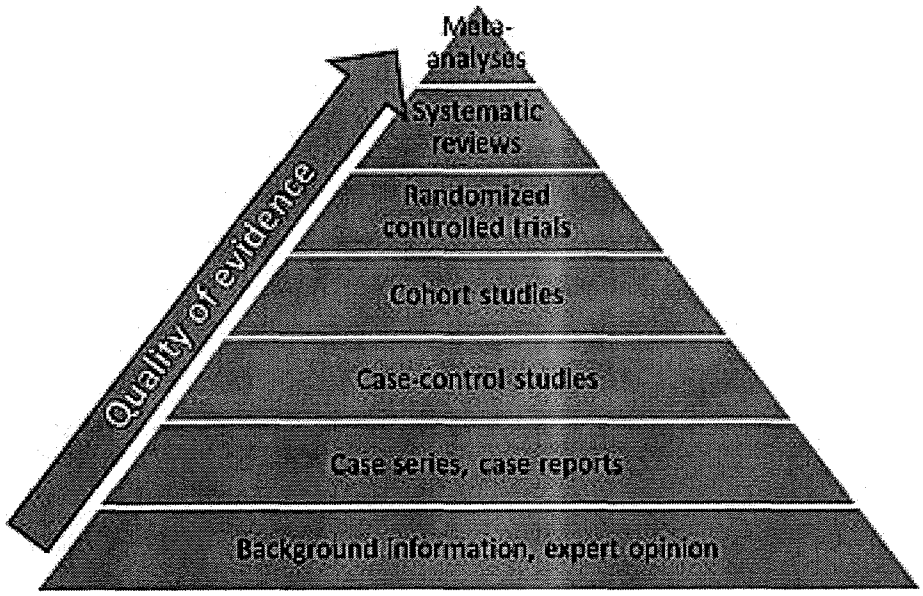
19. Rehman H, Bezerra CC, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database Syst Rev 2011;1:CD001754.]

(Nager, Midurethral slings: evidence-based medicine vs the medicolegal system, Am J Obstet Gynecol June 2016, 708-711.)

C. Evidence from the medical literature – Why we do what we do

Type 1, monofilament, macroporous polypropylene mesh, which describes the mesh used in TVT and TVT-O, is the synthetic material most commonly used in MUS. The synthetic mesh MUS has been broadly adopted and is widely considered the gold standard procedure for SUI in women. The medical literature supports the use of Type 1 monofilament, macroporous polypropylene MUS as either equivalent to or, more often, superior to alternative treatments including Burch colposuspension, autologous pubovaginal slings, and MUS using other sling materials.

TVT been studied in more than 100 randomized controlled trials (RCTs) and TVT-O has been studied in more than 60 RCTs. (April 5, 2013 Email of Medical Director Piet Hinoul and attached study spreadsheets, ETH.MESH.08307644-45) Both have been analyzed in numerous systematic reviews and meta-analyses, which provide the highest level of medical and scientific evidence, and upon which my opinions are based:



(http://www.cebi.ox.ac.uk/for-practitioners/what-is-good-evidence.html)

The Ford 2015 Cochrane Review, for example, analyzed 81 trials that, combined, evaluated 12,113 women, and concluded that the MUS is the most extensively studied surgical treatment for SUI in women and has a good safety profile. Regardless of the route traversed (transobturator or retropubic) MUS have been demonstrated to be highly effective in the short and medium term, with accruing evidence demonstrating their effectiveness also in the long term. The authors noted that their review showed the positive impact of the MUS on improving the quality of life of women who have SUI. Fewer adverse events occurred with the transobturator approach, with the exception of groin pain (which was of short duration), and there was no evidence to support use of one approach over the other. Incidence of complications was determined by analyzing large national registries and voluntary reporting registries or databases, including MAUDE, and complication rates were bladder perforation in 2.7% to 3.9% of cases; reoperation rates relating to tape insertion or postoperative voiding dysfunction in 1.6% to 2.4% of cases; urinary retention in 1.6% of cases; pelvic hematoma in 0.7% to 1.9% of cases; infection rate of 0.7% of cases; vaginal tape erosion/extrusion in 1.5% of cases; and groin pain in 0.4% of cases. Over 80% of women with SUI are cured or have significant improvement in their symptoms with either retropubic or transobturator route MUS for up to five years after surgery. (Ford 2015.)

The Tommaselli systematic review and meta-analysis evaluated long-term outcomes of retropubic approach MUS and medium-term outcomes of transobturator approach MUS (a total of 49 studies, the vast majority of which used TVT and TVT-O MUS). The authors reported high objective and subjective cure rates in the long and medium term, and similar cure rates for retropubic and transobturator approach. The authors found a high safety profile and a limited number of complications which were seldom severe. The most frequently seen complication in both approaches was de novo OAB which is treatable with tape division or anticholinergics. The incidence of pain with the transobturator approach was 6%, which included postoperative, persistent and chronic pain, but all resolved within weeks or months, with no long-term sequelae. The authors further noted that the rate of chronic pain in the groin and/or thigh is even "far lower." No differences were observed between the outside-in obturator approach and the inside-out obturator approach (TVT-O uses the inside-out approach). (Tommaselli, et al, Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and meta-analysis, Int Urogynecol J 2015, 26:1253-68.)

Further evidence on the treatments for SUI and the safety and efficacy of MUS, including additional systematic reviews and meta-analyses, are discussed below.

1. Physical Therapy (PFMT): PFMT vs. MUS

Physical therapy (PFMT), directed at improving pelvic muscle function, is a long-standing non-invasive primary treatment of SUI. Kegel reported improvement of UI in women using pelvic floor strengthening exercises (Kegel AH, Progressive resistance exercise in the functional restoration of the perineal muscles, Am J Obstet Gynecol 1948 56: 238-48). Over the following half-century, instructions for pelvic muscle exercises have been supplemented with biofeedback devices, electrical stimulation, and weighted vaginal cones.

PFMT as a treatment modality for SUI has been compared with both expectant and surgical management. Supervised PFMT results in improvement in SUI symptoms with low risk of adverse events, but absolute cure rates are low. Compared with PFMT, midurethral sling (MUS) surgery results in superior improvement in SUI. Many women with moderate to severe SUI who initiate PFMT ultimately opt for surgical therapy.

Supervised PFMT was compared with MUS as primary treatment of moderate to severe SUI or stress-predominant MUI in a multicenter randomized controlled trial of 460 women (Labrie J et al., Surgery versus physiotherapy for stress urinary incontinence, NEJM 2013 369 (12) 1124-33). PFMT entailed visits supervised by a certified pelvic floor physical therapist over 9 to 18 weeks, and included biofeedback or electrical stimulation at the discretion of the treating provider. Primary outcome was subjective improvement in symptoms (much or very much better) as measured by the Patient Global Impression of Improvement (PGI-I) scale. Subjective and objective cure were secondary outcomes, defined as an absence of SUI symptoms and negative cough stress test at 300 mL respectively. The study design allowed women to cross over from one treatment group to another if they were dissatisfied with the result of their treatment, *and 49% of women initially randomized to PFMT opted for a MUS in the study, whereas 11.2% of women crossed over to PFMT after primary MUS.*

In the intention-to-treat analysis, subjective improvement in SUI symptoms at 12 months was 91% among women who were randomized to MUS, versus 65% following randomization to PFMT. Results were similar for women who underwent MUS as a primary treatment compared with those who crossed over after a trial of PFMT (91% vs 93%, P = .68). However, only *32% of women who received PFMT and did not cross over reported subjective improvement (P<.001).* Subjective and objective cure rates were 85% and 77% for women who underwent initial surgery but only 16% and 44% for women who underwent PFMT (P<.001). Adverse events were exclusively reported in the surgery group and included bladder or vaginal trocar perforation, reoperation for urinary retention or mesh exposure, blood loss greater than 500 mL, hematoma, postoperative bleeding, and new urge urinary incontinence.

2. Fascial Pubovaginal Sling (PVS): Fascial Pubovaginal Sling Versus Midurethral Slings

Outcomes after autologous fascial PVS and retropubic MUS have been compared in five RCTs and a systematic review with meta-analysis, although these studies are limited by small sample sizes and short follow-up.

Schimpf's (SGS) 2014 systematic review and meta-analysis of studies comparing PVS and MUS favored MUS for subjective outcomes (OR 0.40, 95% CI 0.18–0.85), and the authors recommended MUS for women considering PVS vs. MUS. The study found no group differences in adverse events overall, including postoperative overactive bladder symptoms (RMUS 6.9% vs PVS 8.6%), return to the operating room for urinary retention (1.2% vs 3%), or graft erosion (1.9% vs 1.6%). (Schimpf, MO et al, Sling surgery for stress urinary incontinence in women: a systematic review and meta-analysis, Am J Obstet Gynecol 2014, 211:71.31-27.)

A 2011 Cochrane Review analyzed twelve trials comparing traditional sling operations, including autologous fascial pubovaginal slings, with minimally invasive sling operations including TVT. Although traditional slings seemed to be as effective as minimally invasive slings in the short term, they had higher rates of adverse effects. The authors noted that the quality of evidence for the studies was variable, follow-up was short and populations small; particularly for identifying complication rates (Rehman, H., et al., Traditional suburethral sling operations for urinary incontinence in women, Cochrane Database of Systematic Reviews 2011, Issue 1, Art. No.: CD001754.)

A large, historical cohort study that compared medium-term urinary continence rates among women treated with autologous sling or midurethral sling found that patients who received autologous slings had longer suprapubic catheter use, were more likely to require urethrolysis (re-operation), and were more likely to need intermittent self-catheterization after suprapubic catheter removal. After adjustment for history of incontinence surgeries, preoperative diagnosis, BMI and age, patients who had autologous slings had a significantly higher risk of any incontinence compared with women who had a MUS. A higher percentage of midurethral sling patients reported satisfaction (92.0% vs. 78.5%; P = .01), and 68.1% of patients with midurethral slings and only 44.3% of patients with autologous slings reported that they were "completely satisfied" (P = .001) (Trabuco et al., Medium-term comparison of continence rates after rectus fascia or midurethral sling placement, Am J Obstet Gynecol 2009; 200:300.e1-300.e6).

Noting that patient-reported outcomes are increasingly recognized as important metrics in female urology, one study reported the effect of changes in urinary storage symptoms on patient-reported QoL following midurethral sling or autologous fascial sling. The study found that

improvement and resolution of urge symptoms are independently associated with better patient satisfaction (based on VAS) and reduced bother symptoms (UDI-6 and IIQ-7), and that MUS placement was associated with these outcomes, even when controlling for other preoperative factors. Although this study found no difference in overall objective cure rates based on sling type (AF-PVS, 71.9 % vs MUS, 78.2 %, p = 0.315), it found that the MUS group had a significantly higher objective cure rate as a primary, rather than a secondary, procedure (81.9 % vs 70.6 %, p = 0.004). Further, receiving an MUS was independently associated with subjective improvement in UDI-6 (OR 2.96, 95 % CI 1.34–6.54, p = 0.007) and VAS (OR 2.35, 95 % CI 1.27–4.35, p = 0.007) compared with AF-PVS recipients (Padmanabhan, P et al., Change in urinary storage symptoms following treatment for female stress urinary incontinence, Int Urogynecol J, 2016, DOI: 10.1007/s00192-016-2951-6).

3. Burch Colposuspension Versus MUS

The largest multicenter RCT (2002) analyzing Burch colposuspension and retropubic MUS, by Ward and Hilton, randomized 315 women with urodynamic SUI and no detrusor overactivity to either retropubic TVT or to open Burch colposuspension and ultimately validated the MUS as a first line procedure (Ward K and Hilton P., Prospective multicenter randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence, BMJ 2002;325:67). Their primary outcome was a composite objective measure of negative urodynamic stress test and 1-hour pad test. Subjective cure, ascertained by the Bristol Female Lower Urinary Tract Symptoms questionnaire was a secondary outcome. The investigators found no significant difference in objective or subjective cure rates between synthetic mesh midurethral slings and Burch colposuspension at their primary end point of 6 months (66% vs 57%, P = .099; and 59% vs 53%, P = NS). Cure rates remained similar between groups at 2-year and 5-year follow-up, with negative 1-hour pad tests in 81% and 80% at 2 years, although study attrition exceeded 50% by 5 years. (Ward KL et al., Prospective multi-center randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence: Two-year follow up, Am J Obstet Gynecol, 2004 190(2) 324-31) (Ward KL et al, Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up, BJOG 2008 115(2): 226-33). Surgical retreatment of persistent SUI was low and not different between groups (3.4% vs 1.8% for the Burch and RMUS groups respectively). However, the authors noted a high incidence of posterior vaginal wall and vault prolapse following colposuspension that was not seen in the TVT group, and concluded it is likely that colposuspension contributes to the development of vault and posterior wall prolapse. Notably, the study was limited by early recruitment termination, resulting in insufficient power to detect potential differences, and a disproportionate attrition before assigned surgery in the Burch group, which compromised the baseline equivalence of the two groups.

A Cochrane Review to assess the effects of MUS for treatment of SUI or mixed urinary incontinence (MUI) in women has similarly reported equivalent success rates between open Burch and synthetic MUS (82% and 79% respectively, with 6 trials analyzed) (Ogah J, et al., Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women, Cochrane Dat Syst Rev, 2009(4), CD006375. DOI: 10.1002/14651858.CD006375.pub2.) MUS resulted in fewer perioperative complications, less postoperative voiding dysfunction, shorter operative time and hospital stay, and was as effective as open retropubic colposuspension (subjective cure rate at 12 months RR 0.96, 95% CI: 0.90--1.03; at 5 years RR 0.91, 95% CI: 0.74--1.12). MUS resulted in more bladder perforations (6% vs. 1%, RR 4.24, 95% CI: 1.71--10.52).

Clinical outcomes after minimally invasive laparoscopic Burch and synthetic mesh MUS have been reported in 8 studies. The Cochrane group found that objective outcomes favored MUS when compared with laparoscopic Burch (RR 0.88, 95% CI 0.81–0.95), whereas subjective cure rates appeared equivalent (RR 0.91, 95% CI 0.80–1.02), as did the rates of perioperative complications and de novo detrusor overactivity. Procedure time was on average 20 minutes longer in the laparoscopic Burch group. Other disadvantages to laparoscopic Burch procedures include the difficulty of the technique, requirement of general anesthesia, abdominal incisions, and pneumoperitoneum.

Outcomes after open Burch and MUS procedures were reiterated in the systematic review and meta-analysis conducted by the Society for Gynecologic Surgeons (Schimpf 2014). The comparison of MUS with Burch included 10 studies, incorporating retropubic MUS (8 studies), transobturator MUS (2 studies), open Burch (7 studies), and laparoscopic Burch (3 studies). Analysis of perioperative and AE (adverse event) data for the absolute rates of complications per type of surgery showed that MUS result in lower rates of perioperative AEs such as postoperative pain, operating room time, hospital stay, bowel injury, wound infection, and hematomas. The Schimpf meta-analysis also showed that dyspareunia was rare with both the retropubic (<0.001%) and obturator (0.16%) slings and that there was a low rate of return to the OR for erosion for both retropubic MUS (1.9%) and transobturator MUS (1.2%). Rate of return to the OR for urinary retention was also low at 2.7% for retropubic slings and 1.1% rates for transobturator slings. On systematic review, absolute rates of wound infection were higher following Burch procedures (Burch 7%, RMUS 0.75%, TMUS 0.74%). The rate of retreatment and re-operation for persistent incontinence was not summarized.

Based on a systematic literature search performed in 2007, Novara et al produced two systematic reviews and meta-analyses of randomized controlled trials evaluating the efficacy and complication rates of TVT compared with Burch colposuspension, pubovaginal slings, and other midurethral tapes (Novara G et al. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol. 2007;52:663-679) (Novara G, et al., Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a

systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur Urol. 2008;53:288-3). The data from the two meta-analyses showed that TVT was significantly more effective than colposuspension and was followed by similar complication rates; the data also showed that TVT was similar in efficacy to pubovaginal slings, which had significantly higher perioperative morbidity.

In a 2010 update to their previous meta-analyses of the field of MUS, Novara and colleagues identified 39 RCTs involving MUS. Patients receiving MUS had significantly higher overall (odds ratio [OR]: 0.61; confidence interval [CI]: 0.46–0.82; p=0.00009) and objective (OR: 0.38; CI: 0.25–0.57; p<0.0001) cure rates than those receiving Burch colposuspension (OR: 4.94; CI: 2.09–11.68; p=0.00003). (Novara G, et al., Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence, European Urology. 2010 58(2) 218-238).

4. Fascial Pubovaginal Slings Versus Burch Colposuspension

The autologous fascial PVS was compared with open Burch colposuspension in the Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr), a multicenter randomized trial of 655 women with demonstrable SUI or stress-predominant MUI and urethral hypermobility (Albo ME et al., Burch colposuspension versus fascial sling to reduce urinary stress incontinence, NEJM 2007 356(21) 2143-55). Concomitant prolapse surgeries were permitted. Cure of SUI was defined as absence of SUI symptoms, no retreatment of SUI, and a negative stress test. Overall cure criteria additionally included no leakage on a 3-day diary, pad weight increase of less than 15 g on a 24-hour test, and absence of symptoms or retreatment of any type of incontinence. At 2 years, SUI-specific cure rates were 66% for the autologous sling group vs 49% for the Burch group, P<.001, and overall cure rates were 47% for autologous sling vs 38%, for Burch colposuspension, P = .01. 47% of patients who had Burch colposuspension and 63% of patients who had autologous fascial sling experienced adverse events. The failure rate according to SUI-specific criteria was 59% for the Burch group and 40% for the autologous sling group.

At 5 years of follow-up, continence rates diminished to 34% for the autologous sling group and 24% for the Burch group, and at 7 years follow-up, success rates declined further to 27% in the autologous sling group and 13% in the Burch group. (Brubaker L, et al., 5-year continence rates, satisfaction and adverse events of Burch urethropexy and fascial sling surgery for urinary incontinence, J Urol 2012 187(4) 1324-30). In both groups, the average yearly decrease in continence was 6% from the end of SISTEr (year 2 after surgery) to year 5 after surgery. Sling surgery was associated with more urinary retention leading to a 6% reoperation rate for retention or voiding symptoms (vs 0% following Burch), whereas *11% of women in the Burch group pursued surgical retreatment of persistent incontinence (vs 2% following sling; P<.001).*

The SISTEr results reported by Richter et al also showed that the cumulative percent of participants who had undergone surgical re-treatment was 26% in the Burch group (29) and 2% in the sling group (5; p <0.001). Among women who were followed for a minimum of 5 years after Burch colposuspension or pubovaginal fascial sling, prior SUI surgery, being menopausal without HRT, having undergone a Burch procedure and increased postoperative urgency incontinence symptoms were significantly associated with long-term failure and recurrent UI (Richter H, et al., Patient Related Factors Associated with Long-Term Urinary Continence After Burch Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012, 18: 485-489).

5. Retropubic Versus Transobturator Midurethral Sling

Five-year follow-up on a multicenter randomized clinical trial assessing cure and complications rates between TVT and TVT-O found cure rates to exceed 80% for both procedures even when women lost to follow-up were included as failures. Satisfaction rates were high and comparable. Subjective and objective continence outcomes are not significantly different. Among the 254 women assessed, 84.7% in the TVT group and 86.2% in the TVT-O group had a negative stress test, a negative pad test, and no retreatment for stress urinary incontinence. Even when counting all 14 women lost to follow up as failures, the objective success rate was 81.6% in the TVT group and 80.3% in the TVT-O group. Subjective success, defined as treatment completely meeting patients' expectations, was reported by 84.6% of the TVT group and 85.6% in the TVT-O group. 92.6% of women in the TVT group and 88.6% of women in the TVT-O group reported that they would recommend the procedure to a friend. Further, complication rates were low, with no differences in complications between the TVT and TVT-O groups. De novo urgency incontinence was experienced by 3.1% in the TVT group and 2.4% in the TVT-O group. Only five women had de novo urgency symptoms, with three having de novo urge incontinence. 4.6% of participants had postoperative frequency and urgency symptoms of moderate or severe degree in the UDI-6, compared with 28.0% preoperatively. No participants had tissue reaction, erosion, or tape protrusion at 5-yr follow-up. One woman in the TVT-O group had a tape extrusion 1 year postoperatively. One woman had urinary retention leading to sling release. (Laurikainen et al., Five-Year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 65(6):1109-14).

The multicenter trial of midurethral slings (TOMUS) randomized 597 women with stress-predominant urinary incontinence to retropubic MUS (RMUS) or transobturator MUS (TMUS) (Richter HE, et al., Retropubic versus transobturator midurethral slings for stress incontinence, NEJM 2010 362: 2066-76). This was an equivalence trial, in which the two procedures would be considered equivalent if the postoperative success rates decreased to within a predetermined margin of +/- 12%. Objective success required a negative stress test, 24-hour pad test, and no

SUI retreatment, whereas subjective success required absence of SUI symptoms, no leakage on a 3-day diary, and no retreatment. Both measures were primary outcomes and were reported at 12 and 24 months. Extended outcomes were reported at 5 years. At 12 months, only objective success rate met the pre-specified criteria for equivalence (RMUS vs. TMUS 80.8% vs. 77.7%, difference of 3.0% 95% CI -3.6% to 9.6%). At 24 months, neither objective nor subjective success rates met the equivalence criteria. Objective success rates at 24 months were 77.3% and 72.3% (difference 5.1%, 95% CI -2.0% to 12.1%) and subjective success rates were 55.7% and 48.3% (difference 7.4%, 95% CI -0.7% to 15.5%) for RMUS and TMUS respectively. Because the CIs were outside the predetermined range of +/- 12% the two procedures could not be considered equivalent, but the CIs also crossed zero, indicating that the success rates were not significantly different.

In an extended follow-up interval up to 5 years postop, the definition of success was modified to be absence of retreatment and absence of SUI symptoms (Kenton K, et al., 5-year longitudinal followup after retropubic and transobturator mid urethral slings, J Urol 2015, 193:203-210). At that point, success rates for the two MUS routes did not meet equivalence criteria (RMUS vs TMUS 51.3% vs 43.4%, difference 7.9%, 95% CI –1.4% to 17.28%). Although the absolute success rates at each time point and by each definition were higher following RMUS, the differences were not statistically significant.

The groups differed in their adverse event profile. (Brubaker L et al., Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study, Am J Obstet Gynecol 2011 205(5) 498.e1-6). Voiding dysfunction requiring surgical management and bladder perforations occurred exclusively in the RMUS group (3% and 5% vs 0.0%, P<.001 and P = .002), whereas neurologic symptoms (primarily pain) were more common following TMUS (5.4% vs 9.7%, P = .04). All bladder perforations were managed intraoperatively without clinically recognized sequelae through 12 months. Group rates of de novo and persistent urgency incontinence were comparable (RMUS vs TMUS, 0.0% vs 0.3%, P> .99, and 14.1% vs 12.8%, P = .63), mesh complications were similar and infrequent at 4.7% and 3% (RMUS and TMUS respectively). Notably, patient satisfaction was high and similar for both MUS groups (RMUS vs TMUS, 86% vs 90%, P = .52) and adverse events had no effect on subjective or objective surgical success (Wai CY et al., Patient satisfaction after midurethral sling surgery for stress urinary incontinence, Obstet Gynecol 2013 121(5) 1009-16).

Results from more than 20 RCTs comparing retropubic with transobturator MUS were summarized in the Society for Gynecologic Surgeons (SGS) systematic review and meta-analysis, incorporating data from more than 3000 women, also discussed above. (Schimpf 2014.) Although meta-analysis favored RMUS for both objective and subjective cure rates, the findings were not statistically significant (OR 1.18, 95% CI 0.95–1.47; and OR 1.17, 95% CI 0.91–1.51).

Overall satisfaction, reported in 4 studies, was comparable (OR 0.77, 95% CI 0.52–1.13). The authors of the meta-analysis recommended either TMUS or RMUS for cure outcomes. Adverse event profiles were variable, and overactive bladder (OAB) symptoms were more common following RMUS (OR 1.41, 95% CI 1.01–1.98, P = .46), whereas the reoperation rates did not differ for either retention or mesh erosion (RMUS vs TMUS, 1.2% vs 1.1% and 1.9% vs 2.7%; ORs not reported).

6. Bulking agents

There are no published studies that have compared the available bulking agents with a control, so no conclusions can be made regarding the efficacy compared with expectant management of SUI symptoms. In a small 45-patient RCT, Macroplastique injection was compared with a control (treated with written instructions for home-based pelvic floor strengthening) (ter Meulen PH et al., Effects of Macroplastique implantation system for stress urinary incontinence and urethral hypermobility in women, Int Urogynecol J 2009 20(2): 177-83). 63% of Macroplastique recipients reported that their symptoms were cured or markedly improved at 3 months, whereas 21% underwent a repeat bulking injection at 3 months because of treatment failure. Only 9% of controls reported cure or marked improvement (P value not reported). Adverse events were reported only in the Macroplastique group (74% urinary retention and 47% post-procedure dysuria).

Another small trial randomized women with SUI/ISD to pubovaginal sling or Macroplastique. Urodynamic cure at 6 months was 81% following PVS, compared with 9% following Macroplastique (P<.001), and 31% of bulking patients pursued further surgery versus 5% following PVS (P value not reported) (Maher CF et al., Pubovaginal sling versus transurethral Macroplastique for stress urinary incontinence and intrinsic sphincter deficiency: a prospective randomised controlled trial, BJOG 2005, 112(6) 797-801).

D. MUS Complications - Overview

Incontinence has a major impact on a patient's quality of life (QOL) and unfortunately complications may arise from any type of surgery for SUI.

All anti-incontinence surgeries are associated with risks of complications. Risks of all surgeries to treat SUI include:

- Infection
- Urinary problems, including frequency, urgency, dysuria, retention or obstruction, incontinence
- Vaginal scarring

- Bleeding
- Wound complications
- Organ/nerve damage
- Inflammation
- Fistula formation
- Neuromuscular problems in pelvic floor muscles, lower extremities and/or the abdominal area
- Additional surgery or surgeries to treat adverse events
- Recurrence or failure
- Foreign body response to sutures, mesh or other graft material
- Erosion, exposure or extrusion of sutures, mesh or other graft material
- Contraction/shrinkage of tissues
- Acute and/or chronic pain with intercourse
- Acute and/or chronic pain

As is demonstrated by the wealth of scientific literature, these risks of all SUI surgeries are commonly known by trained pelvic floor surgeons.

Several variables have an impact on the specific epidemiology of MUS-related complications and reporting. Lack of worldwide national registries of all MUS procedures means that often investigators/surgeons do not have the denominator for calculating the true incidence of complications and a discrepancy exists between complication rates reported in the literature and independent databases such as the Manufacturer and User Facility Device Experience (MAUDE), which monitors voluntary reporting of MUS-related complications (Deng D et al., Presentation and management of major complications of midurethral slings: Are complications under-reported? Neurourol Urodyn 2007;26:46–52). Other issues that impact epidemiology of complications of MUS include: the varied timing of complications (intraop/immediately postop/delayed postop), follow-up (whether the patient re-presents to the original implanter or to another surgeon for complications), and whether all complications are symptomatic.

In a recent multicenter retrospective study of complications from mesh after surgery for SUI and POP in 347 women, the authors highlighted that women with complications after midurethral sling-only procedures were treated more often with medical therapy and rarely required surgical re-intervention (Abbot S, et al., Evaluation and management of complications from synthetic mesh after pelvic reconstructive surgery: a multicenter study, Am J Obstet Gynecol 2014; 210:163e1-8).

Risk factors for MUS complications can be broadly divided into patient-related, technical or procedure-related, and "mesh-related."

1. Mesh Exposure/ Extrusion[1]

Reported rate for mesh exposure after MUS is variable but low (1-2.5%) (Ford 2015) (Schimpf 2014) and the majority of cases can be managed with topical estrogen.

Hammad et al (Hammad FT et al, Erosions and urinary retention following polypropylene synthetic sling: Australasian survey, Eur Urol 2005; 47:641–7) reported that 35% of vaginal exposures were asymptomatic and exposure was discovered on routine follow-up, not during a visit specifically for a patient complaint. Kobashi et al confirmed these data. In > 90 women who received a polypropylene mesh for the treatment of SUI, 3 developed vaginal exposure, but only 1 had symptoms such as pain, discomfort during sexual activity, and vaginal discharge and exposure was discovered during a routine check-up. (Kobashi KC, et al., Management of vaginal erosion of polypropylene mesh slings, J Urol 2003; 169:2242–3).

Purported patient-centered risk factors for mesh exposure include age, early resumption of sexual activity, estrogen deficiency and severe genital atrophy, prior surgical scarring, diabetes, steroid use, bacterial milieu/colonization/existing preclinical infection, and smoking.

All experienced pelvic surgeons are familiar with these risks, as they are also risks for other pelvic surgeries, including all other incontinence surgeries. Moreover, all surgeons are familiar with prior surgical scarring, diabetes, steroid use, bacterial milieu/colonization/existing preclinical infection, and smoking as risk factors for poor healing after any surgery. Funk et al identified a population-based cohort of 188,454 women who had sling revision/removal for mesh erosion (better described as exposure, although the terms are often used, albeit incorrectly, interchangeably) and retention and found a 9-year cumulative risk of 3.7% (risk of mesh erosion 2.5% vs. 1.3 % for retention). (Funk et al, Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors, Am J Obstet Gynecol 2013; 208:78 e1-7).

In a randomized controlled equivalence trial of TVT and SPARC, Lord et al found a 4.8% extrusion rate for TVT and a 10.5% rate for SPARC. (Lord HE, et al, A randomized controlled equivalence trial of short-term complications and efficacy of tension-free vaginal tape and suprapubic urethral support sling for treating stress incontinence, BJU Int 2006 98 :367-76.)

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[1] While true erosions into an adjacent organ, do occur, the term "erosion" – "the state of being worn away by friction or pressure" – does not suit the scenarios encountered here; use of the term "erosion" where "exposure" is appropriate is discouraged[IUGA/ICS Working Group on Complications Terminology Neurourol Urodyn. 2011 Jan; 30(1):2-12.]

2. Infection

Vaginal surgery is considered ''clean-contaminated surgery'' because the vagina is naturally colonized with bacteria. Normal flora consists of a variety of microorganisms such as Lactobacilli, anaerobic bacteria, Staphylococcus species, Streptococcus species, and Enterococcus faecalis.

Infection is uncommon with type 1 macroporous polypropylene, which is the mesh used in TVT and TVT-O, and is usually linked to other types of material implanted. Infections may occur with or without vaginal mesh exposure. The Ford 2015 Cochrane review analyzing data from thousands of patients found the rate of infection 0.7% and 0.6% for retropubic MUS and obturator MUS respectively. These rates are on par with the 2014 SGS systematic review (Schimpf 2014) which additionally showed comparatively lower rates of infection for MUS than for PV slings and Burch repairs. The mesh in TVT and TVT-O is among the most macroporous in SUI slings and allows for greatest efficacy and biocompatibility.

There are no studies regarding slings and infection rate in the absence of using prophylactic antibiotics – administration of a first generation cephalosporin + - an additional antibiotic for added anaerobic coverage is commonly practiced.

3. Mesh shrinkage / retraction

Controversy is apparent over the existence of mesh shrinkage/retraction as well as over the management of the symptoms and findings. The topic of mesh contraction is debated and commonly (although not necessarily correctly) applied to symptomatic complications following transvaginal mesh placement for POP. It is claimed that mesh contraction may be due to immunological processes rather than surgical methods or technique (Feiner B, Maher C., Vaginal mesh contraction: definition, clinical presentation, and management, Obstet Gynecol 2010 115:325-330). Claims of mesh shrinkage or contraction are typically based on studies using single time points (i.e., not on longitudinal observations on individual patients) (Letouzey V et al., Ultrasound evaluation of polypropylene mesh contraction at long term after vaginal surgery for cystocele repair, Int Urogynecol J 2009 20:s205-6) (Tunn R et al., Sonomorphological evaluation of polypropylene mesh implants after vaginal mesh repair in women with cystocele or rectocele, Ultrasound Obstet Gynecol 2007 29:449-52) (Velemir L et al., Transvaginal mesh repair of anterior and posterior vaginal wall prolapse: a clinical and ultrasonographic study, Ultrasound Obstet Gynecol 2010 35:474-80).

Tunn's small longitudinal study suggested that most of the difference between in vitro and in vivo mesh dimensions was due to surgical technique (i.e. warping or curling of the mesh during or immediately after implantation). It is implausible that biological /immunological processes

would alter appearances of the mesh (react to the mesh) so much within a few weeks. It is likely that there is some degree of wound contraction within months after a mesh implant (similar to wound contraction that is purported after native tissue repairs for POP) (Helstrom L, Nilsson B., Impact of vaginal surgery on sexuality and quality of life in women with urinary incontinence or genital descensus, Acta Obstet Gynecol Scand 2005 84:79-84).

Lo et al, found a 19.6% reduction in the length of mesh for POP repair on ultrasonography at one month postoperatively (Lo TS, One-year outcome of concurrent anterior and posterior transvaginal mesh surgery for treatment of advanced urogenital prolapse: case series, J Minim Invasive Gynecol. 2010 Jul-Aug; 17(4):473-9). Contrary to these findings, Dietz *et al.*, found no evidence of mesh contraction in their longitudinal study of 40 women after transobturator PERIGEE mesh implantation. The authors performed four-dimensional ultrasound at 3-53 months at least twice in each to measure mesh dimensions at two time points after implantation (Dietz HP et al., Mesh contraction; myth or reality? AJOG 2011 204(173) e1-4). Dietz found that mesh length at rest and at valsalva increase by 10% over a period of 18 months on average.

In MUS, Nilsson's prospective follow up at 17 years demonstrated no shrinkage of the TVT MUS over time, indirectly suggested by stable PVR volumes (Nilsson 2013) and Lukacz also indirectly found no shrinkage or tightening, where resting Q-tip angles remained unchanged (Lukacz ES et al., The effects of the tension-free vaginal tape on proximal urethral position: a prospective, longitudinal evaluation, Int Urogynecol J 2003 14:179-84). On the contrary, Nilsson's study demonstrated long-term efficacy and low complications, with objective cure rate of 91.3% and 87.2% of patients considering themselves either cured or significantly better than before surgery. 98% of patients would recommend TVT to a friend.

4. Dyspareunia/ Pain

Chronic pelvic pain and dyspareunia may occur after any SUI surgery and patients should be counseled as such by their surgeons - but we have also seen dyspareunia and sexual dysfunction improve subsequent to MUS placement.

Sexual activity and pain were assessed as part of the TOMUS study. Significant similar improvements in sexual function were seen in both MUS groups. Mean PISQ (Pelvic organ prolapse/urinary incontinence sexual questionnaire) scores increased at baseline at 6 and 24 months. Dyspareunia, incontinence during sex, and fear of UI during coitus improved after surgery. Specifically, pain with intercourse was reported by 38% at baseline and decreased to 27% (at 12 months postop) (p=.003). The analysis was repeated on the 247 women having just a MUS without concomitant procedures (e.g., hysterectomy/POP repair) and dyspareunia decreased from 57% at baseline to 43% at 12 months postop (p = .03). Patient satisfaction was also assessed as part of the TOMUS trial and 95% of participants would have the surgery again

or recommend it to a family member/friend – which is my experience as well (Zyczynski HM et al., Sexual activity and function in women more than 2 years after midurethral sling placement, Am J Obstet Gynecol 2012 207:421 e1-6) (Wai 2013).

Schmipf et al, as part of the SGS meta-analysis, found that dyspareunia was rare with both retropubic and TO slings (<0.001% and .16% respectively).

Sexual function was found to improve in women following TVT and MONARC – no change in dyspareunia or orgasm intensity was found (De Souza et al., Sexual function following retropubic TVT and transobturator Monarc sling in women with intrinsic sphincter deficiency: a multicentre prospective study, Int Urogynecol J 2012 23: 153-8).

So while dyspareunia may occur after MUS, it can be related to malpositioning of the sling in relationship to the mid-urethra, the lateral fornices, and proper depth of placement (although the incidence of malposition in patients without dyspareunia is unknown) (Roth T., Sling removal for dyspareunia: Is sling location a factor? NDPoster presentation at the International Continence Society Mtg, Beijing, 10/2012)

Groin and thigh pain is a potential complication of transobturator mid-urethral sling placement, but is usually self-limited and responds to NSAIDs, physical therapy, anesthetic injections, and, uncommonly, if those fail – explantation. (Roth TM, Management of persistent groin pain after transobturator slings, Int Urogynecol J 2007 18:1371-3). Injury to the obturator neurovascular bundle is uncommon – but careful attention is needed towards proper positioning of the patient and her legs (Atassi Z et al., Haemorrhage and nerve damage as complications of TVT-O procedure: Case report and literature review, Arch Gynecol Obstet 2008 277:161–4). Suprapubic pain (after retropubic MUS) is also very uncommon as is the potential for nerve entrapment/injury (Geis K., Ilioinguinal nerve entrapment after a tension-free vaginal tape (TVT) procedure, Int Urogynecol J 2002 13:136–8).

5. Recall Bias

The phenomena of recall bias reminds us of the importance of objective assessment of patient-reported outcomes of surgery and condition prior to surgery. Recall bias arises when there is intentional or unintentional differential recall (and thus reporting) of an outcome by subjects in one group compared to the other (Grimes D, Schulz K. Bias and causal association in observational research. Lancet 2002; 359: 248-252). Recall bias can inflate patient self-reports of a complication.

Related to the issue of "recall bias" is patients' declining ability to remember the risks they were advised of during the informed consent process. McFadden and colleagues found that surgical risk recall declined from 92% immediately post-consent to 72% at only 6 weeks postoperatively.

Even recall that mesh was placed during patients' procedure declined from 98% to 84% from immediately post-consent to 6 weeks postop. (McFadden B.L. et al., Patient recall 6 weeks after surgical consent for midurethral sling using mesh, Int Urogynecol J 2013, 24:2099-2104.

E. Polypropylene as a biomaterial/Host response to polypropylene

1. Inflammation

In the case of successful MUS implantation, it is currently thought that the material induces an acute inflammatory response, which leads to constructive remodeling and material integration.

Inflammation is an important process not only responsible for clearing a wound of debris and necrotic/abnormal material, but equally crucial for tissue remodeling and regeneration. We should not assume that inflammation related to a biomaterial implant equates to poor patient/surgical outcomes. (Brown BN et al., Macrophage polarization: An opportunity for improved outcomes in biomaterials and regenerative medicine, Biomaterials 33(15): 3792-3802.) The inflammatory response to large pore polypropylene mesh is short lived and is needed for healing and tissue incorporation and normally followed by a long-term process. Most inert biomaterials elicit an early inflammatory response, followed by a late tissue reaction characterized by encapsulation and colonization of the implant by collagen and fibroblasts (Schoen, Biomaterials Science: An Introduction to Materials in Medicine, 3rd Ed., 2013, Tissue Response to Injury: Inflammation, Repair and Regeneration, §II.1, 464-466).

The immune response to any foreign material is complex, dynamic, and patient-specific. The relationship between graft and host tissues will vary for different materials and with different individuals. During development of the TVT, different sling materials were trialed: Teflon, Gore-Tex, Mersilene, the majority leading to tape rejection by the patient. Macroporous monofilament polypropylene has the best track record of host tissue incorporation/integration, safety and biocompatibility. The FDA specifically recognizes that the biocompatibility of Prolene has been established [53 Fed. Reg. 23856 (June 24, 1988)].

Pierce et al reported a long term study comparing biological and synthetic grafts implanted in rabbits. Polypropylene caused a milder inflammatory reaction with more long term, better host tissue incorporation compared to natural grafts (Pierce LM, et al., Long-term histologic response to synthetic and biologic graft materials implanted in the vagina and abdomen of a rabbit model, AJOG 2009 200(5) 546.el–546.e8). Elmer et al, reported an increase in macrophages and mast cell counts and a mild but persistent foreign body response to polypropylene meshes (Elmer C, et al, J Urol 181(3) 1189–1195).

2. Post-implantation changes/ biomechanics

Polypropylene mesh sling implantation creates a wound reaction, then granulation tissue with macrophages, giant cells, lymphocytes and polymorphonuclear leukocytes. This reaction is followed by the creation of collagen III, which in some weeks converts to collagen I, which covers the implanted mesh fibers. (Petros PE, Ulmsten UI and Papadimitriou J: The autogenic ligament procedure: a technique for planned formation of an artificial neoligament. Acta Obstet Gynecol Scand Suppl 1990; 153: 43. 16) It has been documented that polypropylene fibers are entirely encapsulated by collagen within 2 weeks of being implanted (Papadimitriou J and Petros P: Histological studies of monofilament and multifilament polypropylene mesh implants demonstrate equivalent penetration of macrophages between fibrils. Hernia 2005; 9: 75). (Petros PE and Richardson PA: Midurethral Tissue Fixation System sling—a 'micromethod' for cure of stress incontinence—preliminary report. Aust N Z J Obstet Gynaecol 2005; 45: 372)

TVT is amongst the least stiff meshes available as a MUS (Moalli PA et al Int Urogynecol J 2008 19(5) 655-663) and a certain threshold of stiffness is needed in polypropylene slings for positive clinical outcomes (Prien-Larsen JC, et al., Influence of TVT properties on outcomes of midurethral sling procedures: high-stiffness versus low-stiffness tape, Int Urogynecol J Epub 2016 27(7):1039-45.). By contrast, other high stiffness materials may not yield or elongate with a cough and that may increase the likelihood of retention and voiding dysfunction, de novo urgency, and even erosion into the urethra.

3. Lack of Evidence of Degradation and Particle Loss

Critics of TVT MUS state that degraded mesh and particle loss leads to short-term and long-term complications, again without scientific basis to make such a claim. Reliable data in the medical literature does not support this. Although Clave et al, noted that in a minority of explanted polypropylene specimens (various manufacturers) there was evidence of ultrastructural degradation and surface cracking on scanning electron microscopy (SEM), they could not rule out that the effect they were describing was not related to the handling and explantation of the mesh itself (Clave A et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants, Int Urogynecol J 21(2010) 261-270). As all samples were from patients with polypropylene (PP) mesh complications (infection and exposure), one should also wonder whether changes noted in the mesh occurred before or after the exposure/infection. Clavé et al note that despite exhaustive testing, they could not explain their findings. Clavé et al could only perform chemical analysis in only 32 of 84 explants, which is too small a sample for an appropriately powered study and to draw meaningful conclusions. Clavé et al, states "Several hypotheses concerning the degradation of the PP are described. None of these, particularly direct oxidation, could be confirmed in this study."

In other series, mesh was removed for non-infective reasons, and the investigators concluded that no graft degradation had occurred in PP [mesh] material and that autologous and cadaveric fascia

had the most demonstrable graft degradation. (Fletcher SG and Lemack GE: Re: Histologic comparison of pubovaginal sling graft materials: a comparative study. Urology 2008; 72: 721) (Woodruff AJ, Cole EE, Dmochowski RR et al: Histologic comparison of pubovaginal sling graft materials: a comparative study. Urology 2008; 72: 85).

Ong, Thames and White analyzed the morphology of explanted PP mesh using a novel mesh cleaning process and where there was consideration given to the formalin fixation process. At each intermediate cleaning step, light microscopy, Fourier Transform Infrared Spectroscopy, and SEM was performed. Their findings refute the claim that PP is oxidized and they demonstrated non-degraded fibers with no damage also refuting the claim that PP is degraded in vivo. They state that the previously identified "cracked layer" was composed of adsorbed protein coating – "arising from a well-established phenomenon upon implantation". Adsorbed proteins when placed in formalin "crosslinked and formed a hard, brittle, protective composite layer." The authors concluded that their method of cleaning of explanted Prolene meshes and subsequent analyses showed that the mesh did not degrade. (Ong KL et al. The myth: in vivo degradation of polypropylene meshes Int Urogyn J 2016 27: s37-8; Thames SF et al, The myth: in vivo degradation of polypropylene meshes, Int Urogynecol J, 2016, DOI 10.1007/s00192-016-3131-4.)

Purported ultrastructural changes don't have a realizable impact on patient outcomes based on long term follow-up of patients with MUS (Tommaselli GA et al, Efficacy and safety of the trans-obturator TVT-Abbrevo device in normal weight compared to overweight patients affected by stress urinary incontinence, Int Urogynecol J 2015;26 1253-68) (Nilsson 2013).

On March 12, 2014, AUGS-SUFU stated in its FAQs for providers that, "Polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. In recent years, concerns regarding implanted polypropylene degradation have been raised as a result of very high magnification images that show portions of some explanted synthetic meshes with "cracked" surfaces. These surface changes were further hypothesized to lead to adverse clinical outcomes, though this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs. Prospective studies have followed patients with implanted mid-urethral slings for 17 years and show excellent durability and safety of the procedure."

4. Lack of Evidence of Toxicity

If one searches PubMed using the key words polypropylene mesh, vaginal use and toxicity, no studies are found, despite critics of TVT MUS claiming it should not be placed in the vagina, that the bacterial milieu and chemical mediators released from bacteria will degrade the mesh, and that the mesh is cytotoxic upon degradation. This argument for toxicity of polypropylene slings is unsupported by the literature. The Food and Drug Administration (FDA) requires multiple biocompatibility tests, including those for subchronic toxicity for all implanted meshes.

Polypropylene has passed those tests and has been recognized by the FDA as biocompatible [53 Fed. Reg. 23856 (June 24, 1988)].

Critics of the TVT MUS state that on implantation the release of hydrogen peroxide and mediators (if not from bacteria) but from leukocytes/macrophages leads to an oxidative process – which is purported to degrade mesh – but this has not been observed in the absence of infection or erosion (Clave 2010) (Ong 2016).

5. Lack of Evidence of Bacterial Slime/Bio-film

Critics of TVT MUS also state that bacteria commonly contaminate mesh and introduce "bacterial slime." However, prior work reveals that even with tapes sitting in the vagina for 6 to 12 weeks in animals and humans, only "mixed organisms" with scant growth or no growth are cultured (Petros PE, Ulmsten UI and Papadimitriou J: The autogenic ligament procedure: a technique for planned formation of an artificial neoligament. Acta Obstet Gynecol Scand Suppl 1990; 153: 43. 16) (Petros PE and Ulmsten UI: The combined intravaginal sling and tuck operation. An ambulatory procedure for cure of stress and urge incontinence. Acta Obstet Gynecol Scand Suppl 1990; 153: 53) (Petros PE: Development of the intravaginal slingplasty, and other ambulatory vaginal procedures. Doctoral thesis. Perth: University of Western Australia 1999). The reason for this finding is that bacteria are immediately attacked by leukocytes and macrophages and eliminated (Papadimitriou J and Petros P: Histological studies of monofilament and multifilament polypropylene mesh implants demonstrate equivalent penetration of macrophages between fibrils. Hernia 2005; 9: 75).

6. Lack of Carcinogenesis

Tumors related to the implantation of polypropylene mid-urethral slings in humans have never been reported. Tumor formation related to biomaterials in animals is well known to depend more on the physical rather than the chemical configuration of the implant: smooth/large surface areas being carcinogenic and irregular disrupted surfaces / porous surfaces (meshes) lacking in carcinogenicity (Moalli et al., Polypropylene mesh: evidence for lack of carcinogenicity, Int Urogynecol J March 2014). Polypropylene is only used as a mesh in human patients. To date, no mesh site cancers have been reported despite millions of polypropylene MUS having been used since the mid 90s. We can also extrapolate the safety and biocompatibility of Prolene in that it has been in use as suture and hernia mesh for decades. Polypropylene material has been used in general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology for over five decades, in millions of patients in the US and the world (AUGS-SUFU FAQs By Providers, Mid-urethral Slings for Stress Urinary Incontinence, March 12, 2014).

F. Other Materials

1. What about Vypro /Ultrapro mesh ?

Review of the literature reveals few experimental studies (animal / in vitro) (Atmaca AF, et al., Time-dependent changes in biomechanical properties of four different synthetic materials in a rabbit model and the importance in respect to sling surgery, Urol Int 2008 (81): 456-61) (Atis G et al, Tissue reaction of the rat urinary bladder to synthetic mesh materials, Scientific World Journal. 2009 Oct 2;9:1046-51 (2009). Sci World J 2:1046-51) and two clinical studies on mixed mesh materials such as Vypro (polypropylene and absorbable polyglactin) and Ultrapro (polypropylene and absorbable poliglecaprone). Therefore there is insufficient data from which to draw conclusions as to the efficacy and safety of these materials for use in midurethral slings.

A single RCT, from Turkey, studied mixed meshes vs Prolene using a "broad-based" sling and a "vaginal island between the mesh and the urethra." (Okulu E, et al, Use of three types of synthetic mesh material in sling surgery: a prospective randomized clinical trial evaluating effectiveness and complications, Scan J Urol 2013: 47: 217-224.) Their technique of sling placement denoted as a "double forced sling" was also first described by their group (Kayigil O, et al, Double forced sling by combining in situ vaginal wall and Infast pubic bone suburethral stabilization techniques: a new method, J Urol 2002 167: 2481-3) and hasn't been studied beyond these two reports. The size of mesh in what ultimately was a "patch sling" was individualized intraoperatively. Incisions were closed utilizing a pedicled flap of vaginal epithelium. Vaginal erosions occurred in 4.34 % of Vypro, 2.08% of Ultrapro, and 4.25% of Prolene. Urethral erosions didn't occur with Ultrapro, but occurred in 2.17% of Vypro and 2.12% of Prolene slings. Only one clinical study looked at the use of "broad-based" synthetic slings (polypropylene) (Shah DK, et al., Broad based tension-free synthetic sling for stress urinary incontinence: 5-year outcome, J Urol 2003 170: 849-51). Informative and meaningful conclusions cannot be drawn from the Okulu paper given the use of a technique not extensively studied nor utilized and the lack its translatability to MUS.

2. PVDF/Dynamesh

PVDF/Dynamesh is not commercially available in the U.S. for surgical treatment of SUI and the scientific literature cannot support its use in treatment of SUI as it supports use of the TVT line of products. Any claim that PVDF/Dynamesh is an alternative mesh for treatment of SUI is impracticable and without adequate scientific support.

G. IFU, Professional Education Materials and the Patient Brochure

The IFU for the TVT line of products, as well as Ethicon's professional education materials, appropriately warn of the risks of the devices. The IFU is never assumed to be a completely

comprehensive list of every possible adverse complication, such as those that are commonly known to all pelvic surgeons and those that are remote risks. The purpose of the IFU is to provide appropriate risk and benefit information as well as instructions for device use. *The IFU does not replace the informed consent process, clinical judgment, surgical training and experience, and continuing medical education on the part of the surgeon.*

Ethicon's IFUs and professional education materials for the TVT line of products appropriately warn surgeons of associated risks and complications, which pelvic floor surgeons would nevertheless be expected to know given their training and experience. Ethicon's patient brochures, which are used in conjunction with not in lieu of the patient's consultation with her surgeon, also appropriately educate the patient regarding risks/complications of the TVT.

Experienced surgeons are aware of the intraoperative and post-operative risks inherent in the use of surgical mesh. Knowledge of the risks and complications of surgery for SUI is a fundamental part of our surgical training. As experienced pelvic surgeons know, complications can occur during and after all surgeries performed for SUI. As stated herein, the risks of TVT and TVT-O are also risks of other surgeries to treat SUI and are therefore well known to experienced pelvic surgeons.

The risks conveyed in the TVT IFU, and in Ethicon's professional education materials, are appropriate because they accurately reflect the risks reported in peer-reviewed medical literature; are observed by experienced pelvic surgeons such as myself; and are discussed by my peers at medical conferences.

While I have also considered the FDA's Device Labeling Guidance #G91-1 "Blue Book Memo," 21 CFR 801.109(c) on the labeling of prescription devices, as well as Ethicon's Standard Operating Procedure on Labeling, I consider the most important source as to the adequacy of the IFU warnings information to be the peer reviewed medical literature. This is because it is the peer-reviewed literature that provides detailed and scientifically documented information on what adverse events have actually been experienced by women implanted with these devices.